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Hyperbaric oxygen therapy for post-stroke depression: A systematic review and meta-analysis

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ABSTRACT

Objectives: Post-stroke depression (PSD) is common consequence of stroke. However, today the majority of PSD patients remains untreated or inadequately treated, especially in the developing countries. Herein, we performed a meta-analysis to evaluate efficacy and safety of hyperbaric oxygen (HBOT) therapy for PSD.

Patients and methods: Seven electronic databases were comprehensively searched for randomized clinical trials (RCTs) from inception to May 2019. Outcome measures included response rate, depression severity, neurological deficit, physical disability and adverse events.

Results: A total of 27 RCTs involving 2250 participants were identified. Patients in HBOT group had a higher response rate than patients in control group (response rate: 69.4% vs 51.2%, odds ratio [OR] = 2.51, 95% confidence interval [CI] [1.83–3.43], $P = 0.000$). HBOT significantly reduced Hamilton Depression (HAMD) –17 item scores (weighted mean difference [WMD] = −4.33, 95% CI [−4.82 to −3.84], $P = 0.000$), HAMD-24 item scores (WMD = −4.31, 95% CI [−5.01 to −3.62], $P = 0.000$), National Institute of Health Stroke Scale (NIHSS) scores (WMD = −2.77, 95% CI [−3.57 to −1.98], $P = 0.000$), Chinese Stroke Scale (CSS) scores (WMD = −3.75, 95% CI [−5.12 to −2.38], $P = 0.000$) and Modified Scandinavian Stroke Scale (MASSS) scores (WMD = −3.66, 95% CI [−6.26 to −1.06], $P = 0.000$). HBOT also improved Barthel Index (WMD = 10.68, 95% CI [7.98–13.37], $P = 0.000$). In subgroup analysis, Group A of studies with hemorrhage patients accounting for less than 20% achieved more reduction of HAMD 17-item score (WMD = −4.47, 95% CI [−5.17 to −3.77], P = 0.000) than Group B of studies with hemorrhage patients no less than 20% (WMD = −3.73, 95% CI [−4.20 to −3.26], P = 0.000). In addition, patents with HBOT along with antidepressants treatment achieve superior results than patients with antidepressants monotherapy. Patients with HBOT monotherapy achieve a slightly higher response rate than patients with antidepressants monotherapy (OR = 1.29, 95% CI [1.04–1.60], P = 0.000). Besides, HBOT group reported less adverse events (9.6%vs16.6%, $P < 0.05$). The most frequent side-effect of HBOT is ear pain (26 cases).

Conclusion: Based on our pooled analysis, HBOT is effective and safe therapeutic approach for PSD. However, results should be cautiously interpreted due to a relatively poor methodological quality.

1. Introduction

Stroke is a major cause of disability and mortality worldwide. Post-stroke depression (PSD) is a common psychiatric sequela, which affects around one-third of stroke patients. [1] Main symptoms of PSD were depressive mood, sleep disturbance, decreased energy, guilt and even suicidal tendencies [2,3]. Currently, it is becoming increasingly accepted that PSD has a strong association with increased mortality, poor life quality, rehabilitation results and functional outcome of stroke survivors [1,4].

Today the majority of PSD patients remains untreated or inadequately treated. [5] Antidepressants (AD) is mainly pharmaceutical treatment for PSD. However, AD is limited by its poor therapeutic effect and increased incidence of adverse events (AEs). A meta-analysis

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revealed a high incidence of adverse events in central nervous system and gastrointestinal. [6] A recent RCT showed that fluoxetine, a commonly used AD, increased the frequency of bone fracture [7]. As a complementary therapeutic approach for PSD, nonpharmacological therapy including psychotherapy, repetitive transcranial magnetic stimulation, acupuncture, music intervention and hyperbaric oxygen treatment (HBOT), is increasing [8].

HBOT is a therapy providing patient with 100% pure oxygen at a pressure above normal atmosphere. [9] Currently, HBOT is widely used in patients with diseases involving carbon monoxide poisoning, diabetic foot ulcers, traumatic brain injury and vascular dementia [10–13]. A recent fundamental study by Lim et al. suggested that HBOT attenuated neuroinflammation and inhibited action on serotonin uptake, which has beneficial effect on depression [14]. Several clinical studies also confirmed the effectiveness and safety of HBOT in PSD [15,16]. However, a quantitative analysis of currently available evidence is lacking. Thus, we conduct the first systematic review and meta-analysis to evaluate the efficacy and safety of HBOT for PSD.

2. Material and methods

The systematic review and meta-analysis were conducted in accordance with PRISMA checklist [17].

2.1. Search strategy

Seven electronic databases (Pubmed, Embase, Cochrane Library, CNKI, VIP, CBM, Wanfang) were comprehensively searched for randomized controlled trials (RCTs) from their inception to May 17, 2019 by two authors independently, with no language restriction. The following terms were used in combination, “hyperbaric oxygen”, “hyperbaric oxygenation”, “HBOT”, “high pressure oxygen”, “post-stroke depression”, “depression after stroke”, “post-ischemic depression”, “depression after cerebral hemorrhage”, “depression after apoplexy”.

2.2. Including and excluding criteria

Only RCTs were included in the analysis. Case-control studies, case series and case reports were not considered. All participants were definitely diagnosed with PSD, with no restriction on age, gender, race and severity of disease. Patients in treatment group received HBOT alone or in combination with other therapeutic approaches including AD, psychotherapy, acupuncture and music therapy. Patients in control group received placebo or other treatments except for HBOT. Studies with a retrospective nature, irrelevant topics, no controls, duplicated data or insufficient data were also excluded.

2.3. Outcome measures

The primary outcome was response rate, which defined as an over 50% reduction in Hamilton Depression Rating Scale (HAMD) scores after treatment. There are mainly three versions of HAMD (17-, 21-, and 24-item version). Depression severity quantified by HAMD was also considered as primary outcome. The secondary outcome included depression severity quantified by Zung Self-Rating Depression Scale (SDS), neurological deficit quantified by National Institute of Health Stroke Scale (NIHSS), Chinese Stroke Scale (CSS) and Modified Edinburgh-Scandinavian Stroke Scale (MESSS), physical disability determined by Barthel Index (BI), and reported adverse events.

2.4. Data extraction

A pre-defined Excel form was used for data collection. Extracted information included the first author’s name, year of publication, study period, age, gender, sample size, withdraws, dropouts, interventions, follow-up and outcome measures. We directly contracted the first or correspondence author by e-mail for insufficient or ambiguous data. Discrepancies were resolved by team discussion.

2.5. Methodological quality

Methodological quality was evaluated by Cochrane Collaboration’s risk of bias tool [18,19]. Each study was categorized into “low”, “unclear” and “high” risk of bias by two reviewers base on following domains: random sequence generation, allocation concealment, blinding to participants, researchers and outcome evaluators, incomplete data, selective outcome reporting and other sources of bias.

2.6. Statistical methods

Statistical analysis was performed by Review Manager 5.0 and STATA 12.0. Dichotomous data was presented as odds ratios (OR) with 95% confidence intervals (CI), while continuous data was presented as weighted mean differences (WMD) with 95% CI. Heterogeneity among studies was assessed by I^2 statistic and Cochrane Q test. A fixed-effect model was utilized for meta-analysis if $I^2 < 50\%$ or $P > 0.10$. Otherwise, a random-effect model was used ($I^2 > 50\%$ or $P < 0.10$). A univariate meta-regression was conducted to assess the influence of stroke type, does and gender on measured outcomes. A funnel plot and Egger’s test was used to assess the publication bias. A sensitivity analysis was performed to explore potential sources of heterogeneity.

3. Results

3.1. Literature search and study characteristics

Totally 248 articles were identified. We removed 89 duplications and excluded another 89 records after screening the title and abstract. Thus, 70 full-text articles were further assessed for eligibility. As shown in Fig.1, we excluded studies with irrelevant topics (n = 13), reporting inappropriate outcome measures (n = 17), not RCTs (n = 11), duplicated data (n = 8), insufficient data (n = 2) and reviews (n = 2). Finally, 27 RCTs [15,20–45] involving 2250 participants (1140 in HBOT group and 1110 in control group) were included for meta-analysis. Detailed characteristics of included trials were descripted in Table 1. All studies were published from 2006 to 2018. The sample size varied from 45 to 200. A total of 22 trials reported diagnostic criteria of depression in accordance with Chinese Classification of Mental Disorders third version (CCMD-3), and 2 studies [38,43] reported criteria of Chinese Classification of Mental Disorders second version (CCMD-2). Depression severity was quantified by HAMD 17-item version in 21 studies, and HAMD 24-item version in 4 studies [15,22,28,30]. All trials reported details of patient selection by CT/MRI evaluations. Sixteen studies reported stroke type of participants but only 2 studies reported location or side of lesions. Among 27 trials, three comparisons were conducted between the treatment group and control group, involving adjuvant HBOT + AD vs. AD (17 studies), HBOT monotherapy vs. AD monotherapy (5 studies) and HBOT + conventional treatment vs. conventional treatment (5 studies). Detailed conventional treatment regimen includes aspirin, mannitol, mecobalamin and calcium channel blockers.

3.2. Methodological quality assessment

Methodological quality of included studies was summarized in Fig. 2. Only 8 studies [21,23,24,26,29,31,32,35] descripted detailed randomization methods. Only 1 study29] provided information of blinding to participants. Five studies [15,22,28,37,44] provided follow-up data including withdraws and drop outs. None reported allocation concealment. None of studies were at risk of selective outcome reporting. Twenty-five studies reported that HBOT group and control group have comparable baseline data.

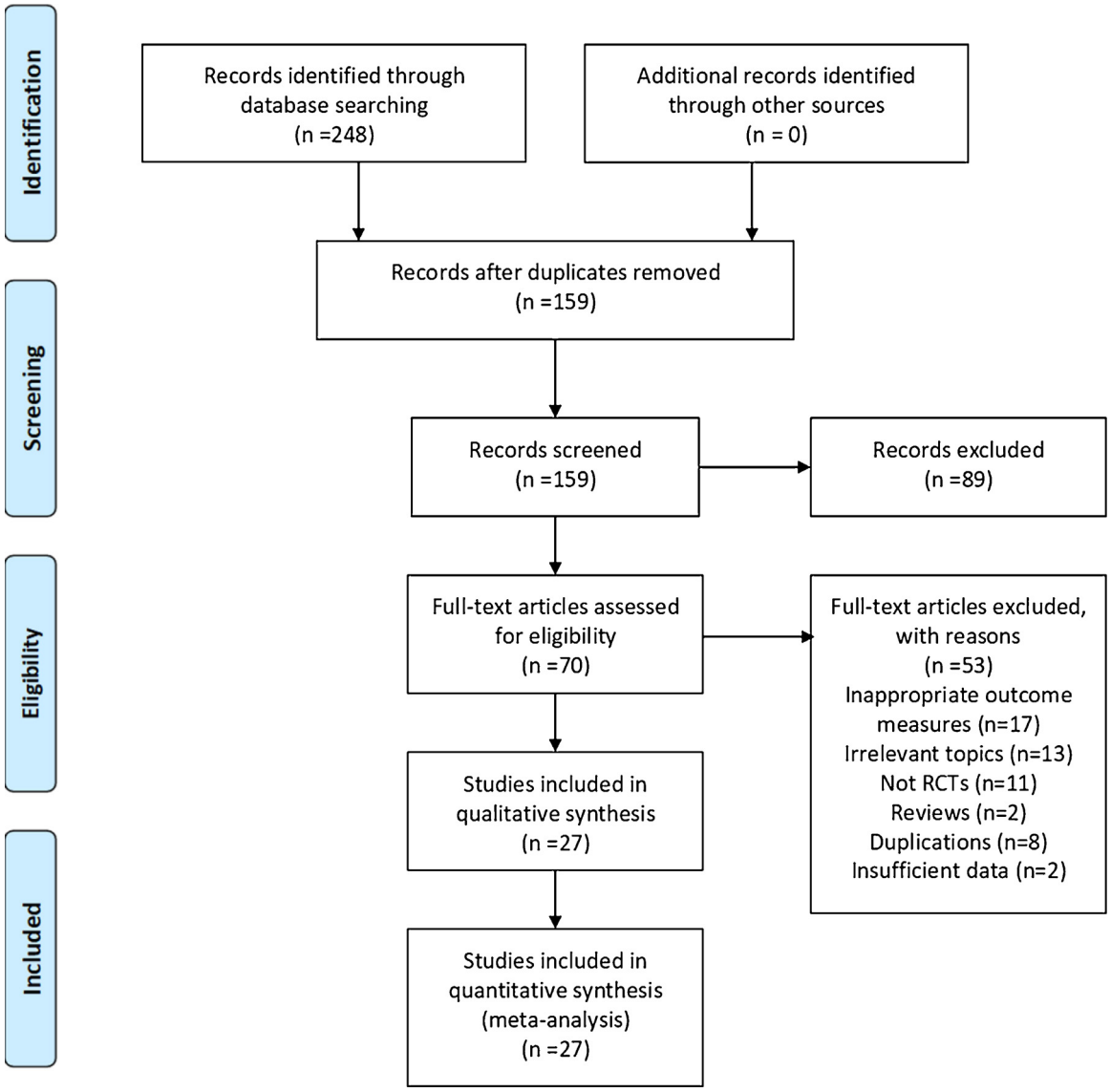

Fig. 1. Flowchart of study selection in accordance with PRISMA checklist.

3.3. Response rate

Nine studies [15,20–23,25,27,28,30] reported response rate. There was no heterogeneity between studies ($I^2 = 0$, $P = 0.658$), therefore a fixed-effect model was performed. The results indicated that patients in HBOT group had a significantly higher response rate compared with patients in control group (response rate: 69.4%vs51.2%, OR = 2.51, 95% CI [1.83–3.43], $P = 0.000$; Fig. 3).

3.4. Effect of HBOT on depression severity

Twenty-five studies employed HAMD scale to evaluate depression severity (21 studies used HAMD 17-items and 4 studies used HAMD 24-items). The results revealed that compared with patients in control group, patients in HBOT group were associated with a more reduced HAMD 17-item scores (WMD = − = −4.33, 95% CI [−4.82 to −3.84], $P = 0.000$; Fig. 4) and HAMD 24-item scores (WMD = − = −4.31, 95% CI [−5.01 to −3.62], $P = 0.000$; Fig. 5), respectively. Besides, one study [24] used SDS to assess depression severity. Their results demonstrated that patients in HBOT group had a more reduced SDS scores after rehabilitation treatment ($P < 0.01$).

3.5. Effect of HBOT on the level of neurological deficit

Nine studies [15,21–23,31–34,38] assessed patients' neurological deficit by using NIHSS. Compared with patients in control group, patients in HBOT group were associated with a more reduced NIHSS scores (WMD = − = −2.77, 95% CI [−3.57 to −1.98], $P = 0.000$; Fig. 6), with moderate heterogeneity ($I^2 = 69.3\%$, $P < 0.01$). Four studies [26,40,41,43] used CSS scale, the results indicated that patients in HBOT group were associated with a more reduced CSS scores (WMD = − = −3.75, 95% CI [−5.12 to −2.38], $P = 0.000$; Fig. 7), with no heterogeneity ($I^2 = 0$, $P = 0.496$). Another three studies [27,37,44] used MESSS scale, HBOT patients were significantly correlated with more reduced MESSS scores (WMD = − = −3.66, 95% CI [−6.26 to −1.06], $P = 0.000$; Fig. 8), with a high heterogeneity ($I^2 = 80.0\%$, $P < 0.01$).

3.6. Effect of HBOT on physical disability

Physical disability was quantified by BI in 11 studies [21,24–27,29,31,32,37,41,44]. Patients in HBOT group were associated with significantly higher BI scores than patients in control group (WMD = 10.68, 95% CI [7.98–13.37], $P = 0.000$; Fig. 9), with a high

Table 1
Baseline characteristics of 27 included studies.

Study ID	Study period	Sample size		Age (years)		CT/MRI evaluation	Hemorrhage	Diagnostic criteria	HAMD versions	Intervention		Duration (days)	Outcome measures
		T (M/F)	C (M/F)	T	C		event%			T	C		
Jiao [20]	2016–2017	46 (25/21)	32 (17/15)	54.9 ± 6.5	56.1 ± 5.1	Yes	0%	CCMD-3	17-items	HBOT (70 min, qd, 0.2Mpa) + CT	CT	36	eq \o\ac(○,1)eq \o\ac(○,2)
Huang [21]	2014–2016	48 (15/33)	48 (17/31)	51.4 ± 5.4	50.8 ± 5.7	Yes	20.8%	CCMD-3	17-items	HBOT (100 min, qd, 0.2Mpa) + Citalopram (20 mg, qd, PO)	Citalopram (20 mg, qd, PO)	42	eq \o\ac(○,1)eq \o\ac(○,2)eq \o\ac(○,3)eq \o\ac(○,6)
Lin [22]	2015–2017	56 (32/24)	57 (30/27)	62.0 ± 3.0	64.0 ± 4.0	Yes	–	CCMD-3	24-items	HBOT (70 min, qd, 0.2Mpa)	Fluoxetine (20 mg, qd, PO)	28	eq \o\ac(○,1)eq \o\ac(○,2)eq \o\ac(○,3)eq \o\ac(○,9)
Chen [23]	2011–2015	30 (12/18)	30 (14/16)	60.7 ± 6.7	62.4 ± 5.9	Yes	45%	CCMD-3	17-items	HBOT (90 min, qd, 0.2Mpa) + Citalopram (20 mg, qd, PO)	Citalopram (20 mg, qd, PO)	60	eq \o\ac(○,1)eq \o\ac(○,2)eq \o\ac(○,3)
Zhu [24]	2013–2015	30 (21/9)	30 (22/8)	57.7 ± 8.6	58.2 ± 9.2	Yes	41.7%	CCMD-3	17-items	HBOT (90 min, qd, 0.12Mpa) + Deanxit (10.5 mg, bid, PO)	Deanxit (10.5 mg, bid, PO)	28	eq \o\ac(○,2)eq \o\ac(○,6)eq \o\ac(○,8)eq \o\ac(○,9)
Gao [25]	2011–2015	100 (41/59)	100 (43/57)	62.3 ± 4.2	62.1 ± 4.8	Yes	0%	CCMD-3	17-items	HBOT (60 min, qd, 0.22Mpa) + Deanxit (10.5 mg, bid, PO)	Deanxit (10.5 mg, bid, PO)	30	eq \o\ac(○,1)eq \o\ac(○,2)eq \o\ac(○,6)
Lei [26]	2013 − 2015	35 (22/13)	35 (20/15)	61.4 ± 9.5	59.7 ± 9.2	Yes	100%	CCMD-3	–	HBOT (110 min, qd, 0.22Mpa) + CT	CT	30	eq \o\ac(○,4)eq \o\ac(○,6)
Sun (2015) [27]	2012–2013	68 (−/−)	68 (−/−)	40.3 ± 5.1	40.3 ± 5.1	Yes	–	CCMD-3	–	HBOT (80 min, qd, 0.2Mpa)	Paroxetine (20 mg, qd, PO)	42	eq \o\ac(○,5)eq \o\ac(○,6)eq \o\ac(○,9)
Lin [28]	2013–2014	27 (16/11)	29 (15/14)	61.0 ± 4.0	62.0 ± 5.0	Yes	–	CCMD-3	24-items	HBOT (70 min, qd, 0.2Mpa)	Fluoxetine (20 mg, qd, PO)	28	eq \o\ac(○,1)eq \o\ac(○,2)eq \o\ac(○,9)
Mao [29]	2012–2013	40 (18/22)	40 (19/21)	55–78	56–78	Yes	0%	CCMD-3	17-items	HBOT (60 min, qd, 0.22Mpa) + Deanxit (10.5 mg, bid, PO)	Deanxit (10.5 mg, bid, PO)	30	eq \o\ac(○,2)eq \o\ac(○,6)eq \o\ac(○,9)
Hu [30]	2013–2014	30 (12/18)	30 (14/16)	62.1 ± 9.0	62.0 ± 9.7	Yes	28.3%	CCMD-3	24-items	HBOT (120 min, qd, 0.2Mpa) + CT	CT	20	eq \o\ac(○,1)eq \o\ac(○,2)eq \o\ac(○,7)
Meng [31]	2010–2012	50 (28/22)	50 (26/24)	62.9	63.1	Yes	45%	–	17-items	HBOT (115 min, qd, 0.2Mpa) + Citalopram (20 − 40 mg, qd, PO)	Citalopram (20 − 40 mg, qd, PO)	28	eq \o\ac(○,2)eq \o\ac(○,3)eq \o\ac(○,6)eq \o\ac(○,9)
Cao [15]	2009–2011	30 (11/19)	30 (12/18)	57 ± 13	56 ± 17	Yes	100%	CCMD-3	24-items	HBOT (80 min, qd, 0.2Mpa) + Deanxit (10.5 mg, bid, PO)	Deanxit (10.5 mg, bid, PO)	28	eq \o\ac(○,1)eq \o\ac(○,2)eq \o\ac(○,3)
Liu [32]	2009–2011	48 (31/17)	48 (29/19)	60.0 ± 7.0	60.0 ± 8.0	Yes	47.9%	CCMD-3	17-items	HBOT (90 min, qd, 0.2Mpa) + Sertraline (50-100 mg, qd, PO)	Sertraline (50 − 100 mg, qd, PO)	28	eq \o\ac(○,2)eq \o\ac(○,3)
Wan [33]	2006–2011	100 (−/−)	90 (−/−)	68.0 ± 7.5	68.0 ± 7.5	Yes	12.5%	CCMD-3	17-items	HBOT (105 min, qd, 0.12Mpa) + Fluoxetine (20 mg, qd, PO)	Fluoxetine (20 mg, qd, PO)	28	eq \o\ac(○,2)eq \o\ac(○,3)
Liu [34]	2009–2011	46 (-/-)	40 (-/-)	64.2 ± 6.8	64.2 ± 6.8	Yes	–	CCMD-3	–	HBOT (90 min, qd, 0.3Mpa) + Duloxetine (60 mg, qd, PO)	Duloxetine (60 mg, qd, PO)	42	eq \o\ac(○,3)eq \o\ac(○,7)
Li [35]	2011–2012	32 (−/−)	32 (−/−)	60.0 ± 2.0	60.0 ± 2.0	Yes	–	CCMD-3	17-items	HBOT (90 min, qd, 0.2Mpa) + Paroxetine (10 − 40 mg, qd, PO)	Paroxetine (10 − 40 mg, qd, PO)	90	eq \o\ac(○,2)
Liu [36]	2006–2010	36 (21/15)	36 (23/13)	62.0 ± 9.0	64.0 ± 8.0	Yes	23.6%	CCMD-3	17-items	HBOT (90 min, qd, 0.2Mpa) + Sertraline (50 − 100 mg, qd, PO)	Sertraline (50 − 100 mg, qd, PO)	42	eq \o\ac(○,2)

(*continued on next page*)

Table 1 (*continued*)

Study ID	Study period	Sample size		Age (years)		CT/MRI evaluation	Hemorrhage event%	Diagnostic criteria	HAMD versions	Intervention		Duration (days)	Outcome measures
		T (M/F)	C (M/F)	T	C					T	C		
Pan [37]	2006–2008	32 (-/-)	32 (-/-)	60.4 ± 8.8	60.4 ± 8.8	Yes	–	CCMD-3	17-items	HBOT (80 min, qd, 0.2Mpa)	Paroxetine (20 mg, qd, PO)	42	eq \o\ac(○,2)eq \o \ac(○,5)eq \o\ac (○,6)eq \o\ac(○,9)
Zhao [38]	2004–2008	30 (−/−)	30 (−/−)	61.9 ± 9.9	61.9 ± 9.9	Yes	–	CCMD-2		HBOT (105 min, qd, 0.12Mpa) + Paroxetine (20 mg, qd, PO)	Paroxetine (20 mg, qd, PO)	60	eq \o\ac(○,2)eq \o \ac(○,3)
Liu [39]	2008–2008	22 (15/7)	23 (15/8)	66.2 ± 14	65.8 ± 11	Yes	–	–	17-items	HBOT (100 min, qd, 0.2Mpa) + Antidepressants (no details)	Antidepressants (no details)	56	eq \o\ac(○,2)
Jiang [40]	2000–2008	42 (26/16)	40 (24/16)	58 ± 19.6	57 ± 18.5	Yes	45.1%	CCMD-3	17-items	HBOT (100 min, qd, 0.16 − 0.2Mpa) + Fluoxetine (no details)	Fluoxetine (no details)	49	eq \o\ac(○,2)eq \o \ac(○,4)
You [41]	2007–2009	30 (13/17)	30 (15/15)	67.8 ± 8.2	68.5 ± 7.3	Yes	–	CCMD-3	17-items	HBOT (105 − 115 min, qd, 0.22Mpa) + Deanxit (10.5 mg, bid, PO)	Deanxit (10.5 mg, bid, PO)	28	eq \o\ac(○,2)eq \o \ac(○,4)eq \o\ac (○,7)
Wang [42]	2006–2007	32 (−/−)	32 (−/−)	–	–	Yes	–	–	17-items	HBOT (120 min, qd, 0.2Mpa) + CT	CT	30	eq \o\ac(○,2)
Lin [43]	2000–2005	27 (16/11)	25 (14/11)	57 ± 19.2	56 ± 18.1	Yes	40.4%	CCMD-2	17-items	HBOT (90 min, qd, 0.16 − 0.2Mpa) + Fluoxetine (no details)	Fluoxetine (no details)	49	eq \o\ac(○,2)eq \o \ac(○,4)
Chen [44]	2000 − 2005	40 (−/−)	40 (−/−)	62.4 ± 9.7	62.4 ± 9.7	Yes	–	CCMD-3	17-items	HBOT (70 min, qd, 0.2 Mpa) + Fluoxetine (20 mg, qd, PO)	Fluoxetine (20 mg, qd, PO)	60	eq \o\ac(○,2)eq \o \ac(○,5)eq \o\ac (○,6)eq\o\ac(○,9)
Liu [45]	–	33 (19/14)	33 (20/13)	68.9 ± 6.7	62.3 ± 6.4	Yes	27.3%	CCMD-3	17-items	HBOT (115 − 120 min, qd, 0.2 Mpa) + CT	CT	25	eq \o\ac(○,2)

HBOT: hyperbaric oxygen treatment; CT: conventional treatment (including aspirin, mannitol, mecobalamin and calcium channel blockers); CCMD: Chinese Classification of Mental Disease criteria; Outcome measures: Response rate, HAMD scores, NIHSS scores, CSS scores, MESSS scores, BI scores, ADL scores, SDS scores, Adverse events.

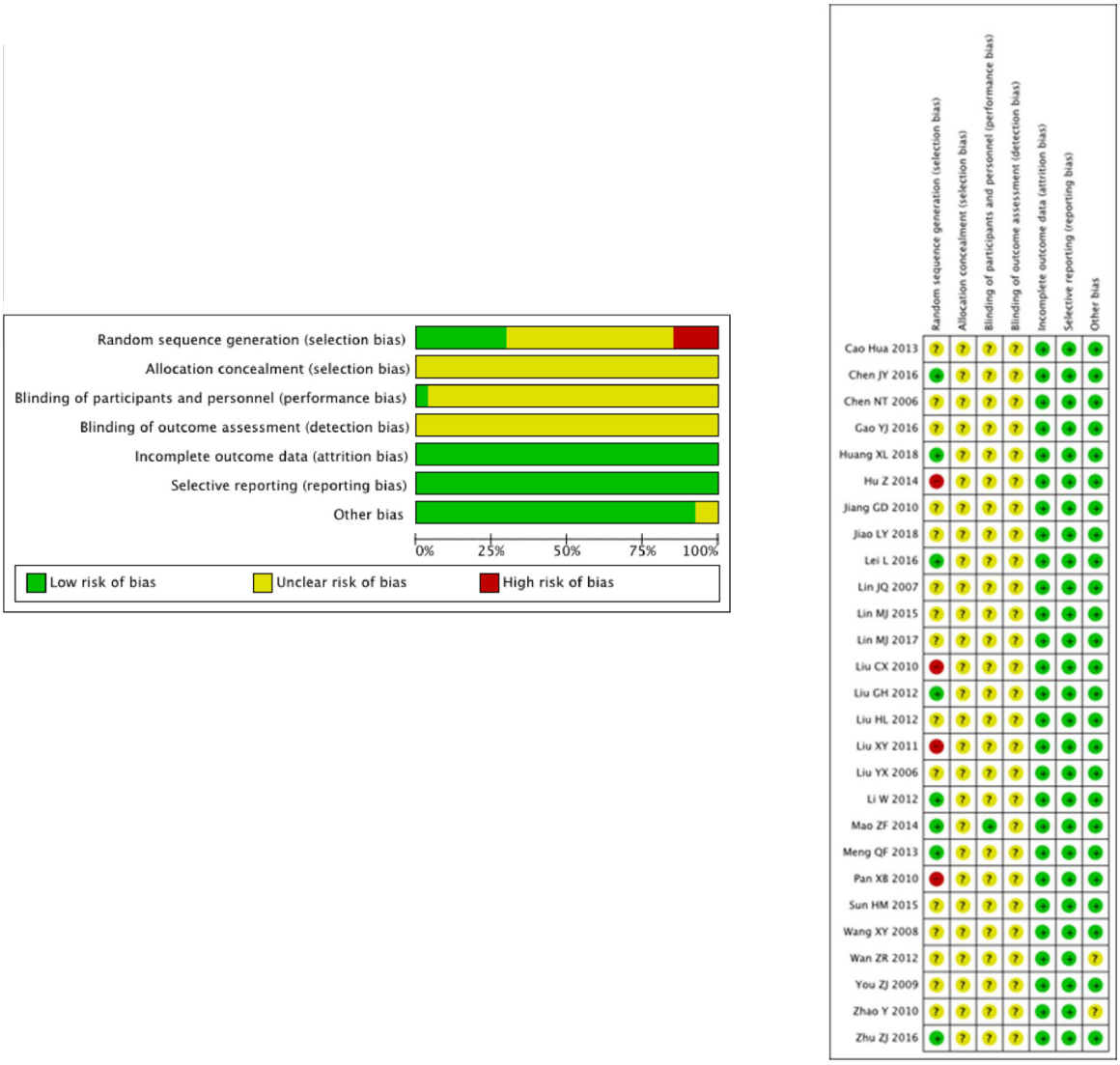

Fig. 2. Risk of bias evaluation of 27 RCTs: (a) risk of bias graph, (b) risk of bias summary.

heterogeneity (I^2 = 90.3%, $P < 0.01$).

3.7. Influence of stroke type

Univariate meta-regression was conducted to assess the influence of stroke type on the outcomes of HBOT treatment. As shown in Table 2, participants with different stroke types achieved significantly different response rate, HAMD-17 score, and BI score after HBOT treatment (all $P < 0.05$). Subsequently we divided all included studies into two subgroups, Group A: studies with hemorrhage patients accounting for less than 20% and Group B: studies with hemorrhage patients accounting for no less than 20%. Subgroup analysis revealed that the effect size was different in two subgroups: Group A (WMD = − = −4.47, 95% CI [−5.17 to −3.77], P < 0.05; Fig. S1) and Group B (WMD = − = −3.73, 95% CI [−4.20 to −3.26], P < 0.05; Fig. S2).

3.8. Dose effect

A univariate meta-regression was performed to evaluate the effect of the number and duration time of HBOT treatment. As shown in Table 3, we found the number of HBOT treatment have no effect on response rate, HAMD-17 score, NIHSS score and BI score (all $P > 0.05$). However, the results revealed that the duration time of HBOT treatment have significant effects on HAMD-17 score, NIHSS score and BI score (all $P < 0.05$), as listed in Table 4.

3.9. Gender effect

Meta-regression was conducted to assess the gender effect. As shown in Table 5, no significant associations were found between gender and response rate, HAMD-17 score, NIHSS score or BI score (all $P > 0.05$).

3.10. HBOT + antidepressants vs antidepressants

In the pooled analysis, patients receiving HBOT plus antidepressants treatment had a significantly higher response rate compared with patients receiving antidepressants alone (OR = 1.46, 95% CI [1.22–1.74], P < 0.01; Fig. 10A). Patients receiving HBOT plus antidepressants also achieved a more reduced HAMD-17 score (WMD = − = −4.33, 95% CI [-4.70 to -3.97], $P < 0.01$; Fig. 10B), a more reduced NIHSS score (WMD = −2.43, 95% CI [−2.90 to −1.97], $P < 0.01$; Fig.10C) and a significant higher BI score (WMD = 8.87, 95% CI [7.81–9.93], $P < 0.01$; Fig. 10D).

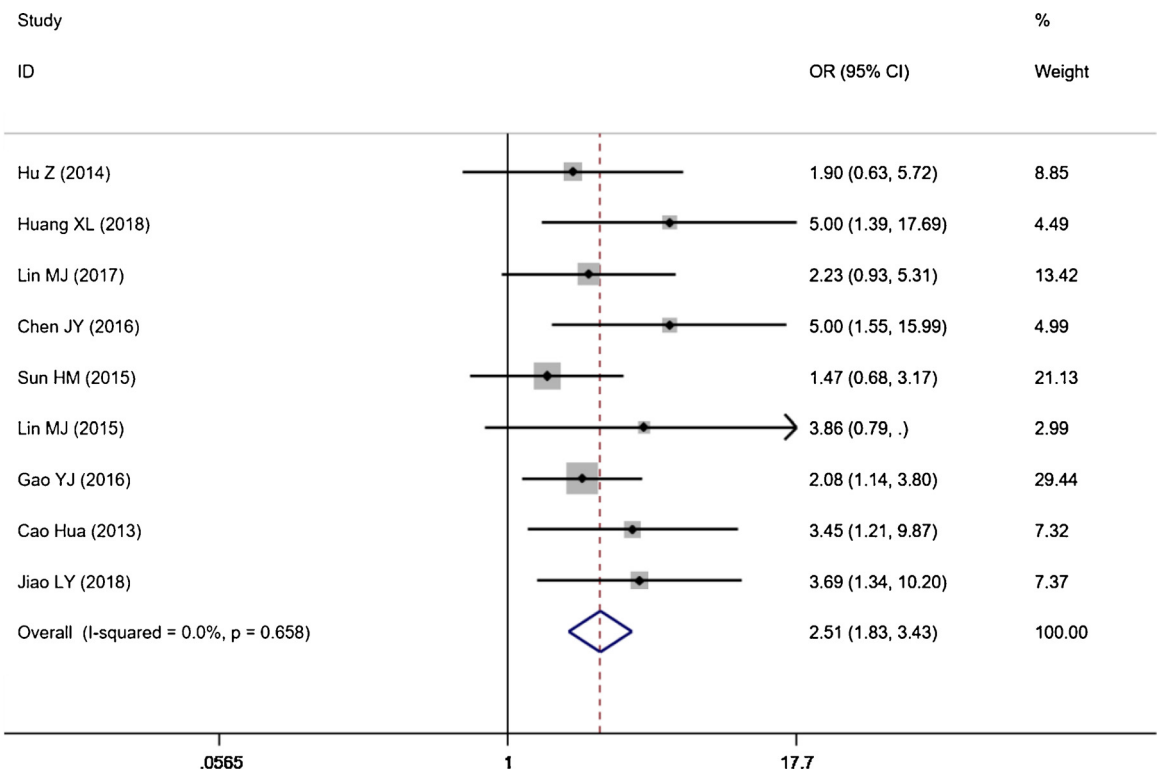

Fig. 3. Forest plot of response rate.

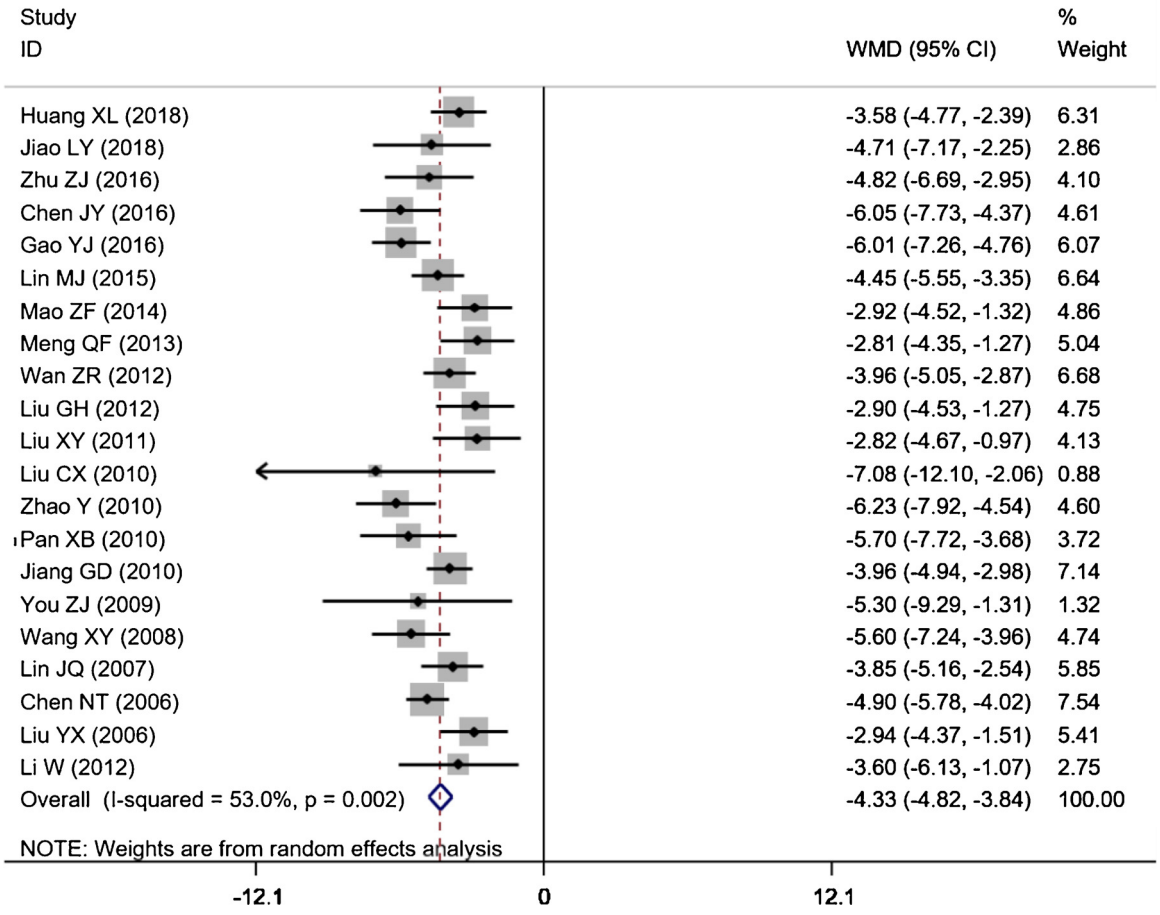

Fig. 4. Forest plot of HAMD 17-item score.

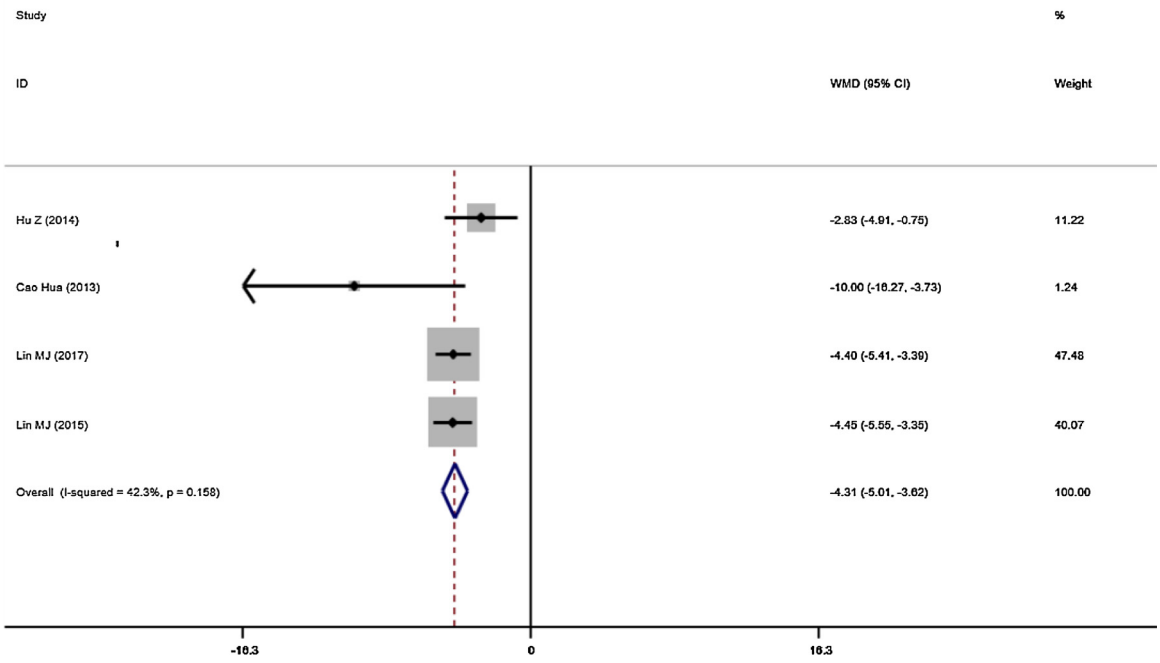

Fig. 5. Forest plot of HAMD 24-item score.

3.11. HBOT vs. Antidepressants

By pooling a meta-analysis, we found that patients receiving HBOT monotherapy had a slightly higher response rate compared with patients receiving antidepressants monotherapy (OR = 1.29, 95% CI [1.04–1.60], P < 0.01; Fig. 11).

3.12. Adverse events

Seven studies [22,24,27–29,37,44] reported AEs. The incidence of AEs in HBOT group was lower than that in control group (9.6% vs 16.6%, $P < 0.05$). The most frequent AEs for HBOT was "ear pain" (26/293) due to barotrauma. No psychological symptoms such as claustrophobia were observed. The main side effects in control group were dizziness (10/296), insomnia (10/296), gastrointestinal disorders (9/296), fatigue (7/296), and moderate headache (6/296).

3.13. Sensitivity analysis and publication bias

We performed a sensitivity analysis for outcomes of response rate,

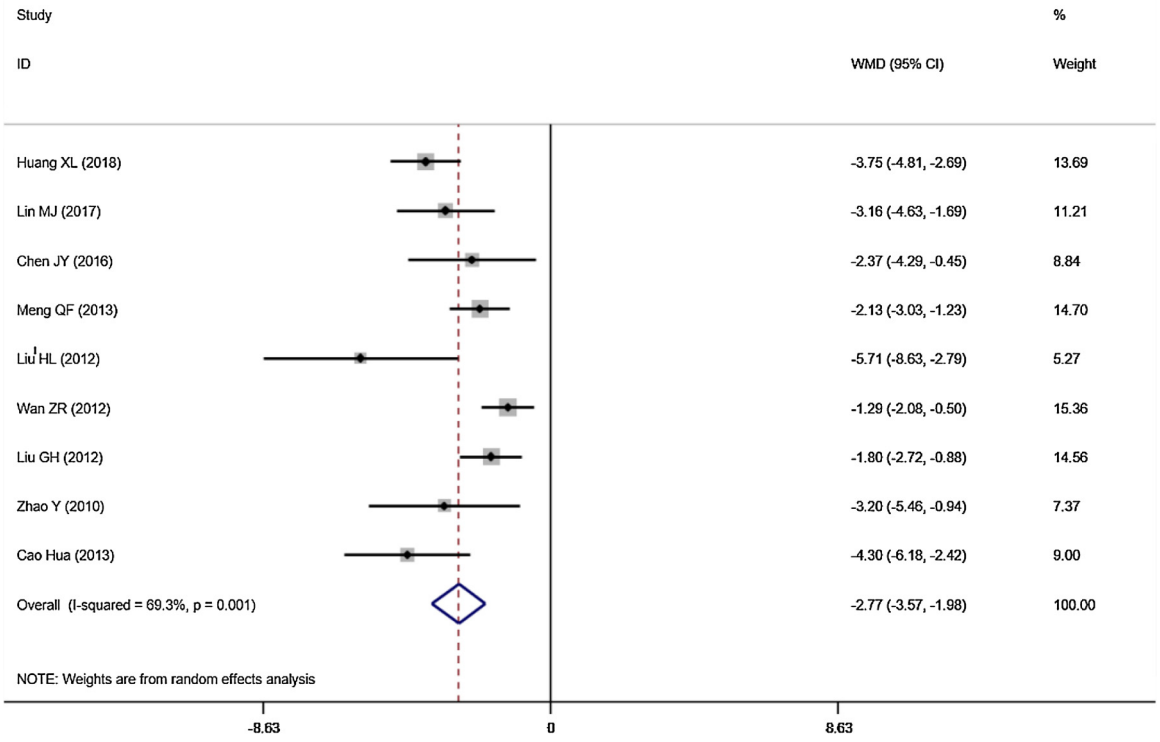

Fig. 6. Forest plot of NIHSS score.

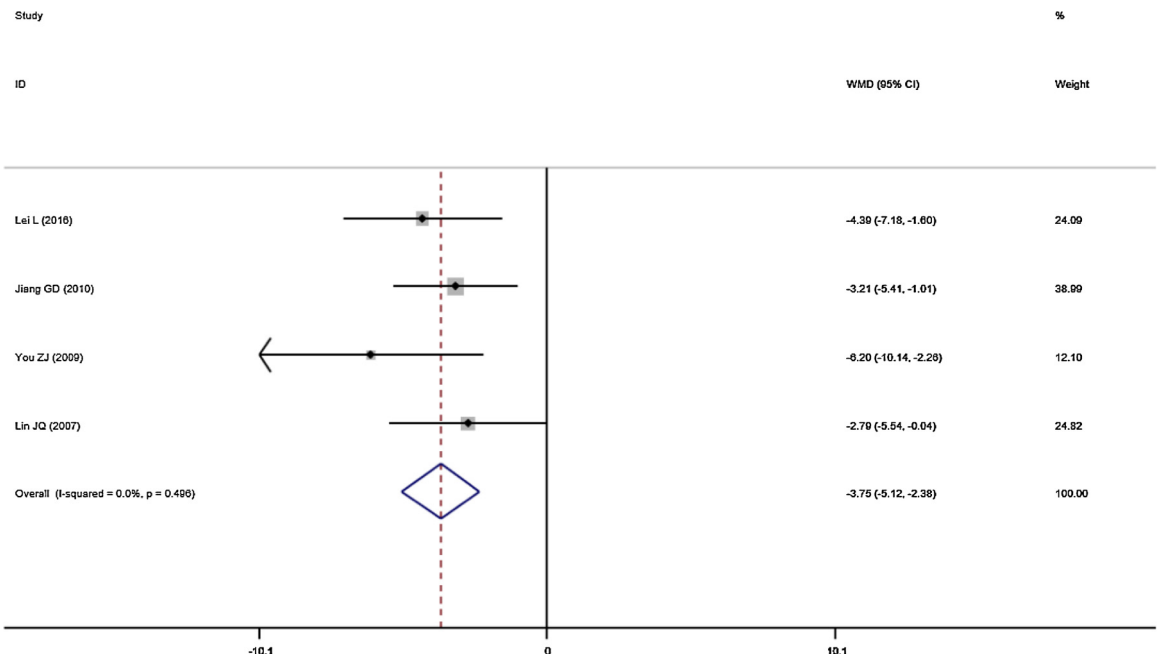

Fig. 7. Forest plot of CSS score.

HAMD 17-item score, NIHSS score and BI score. As shown in Fig. 12, after removing each study, the pooled results remained stable, indicating the results were reliable and with no potential sources of heterogeneity. In addition, we use Egger's test to calculate publication bias. As presented in Fig. 13, all $P > 0.05$ of Egger's test suggested of no obvious publication bias.

4. Discussion

To our knowledge, this is the first systematic review and meta-analysis to evaluate the efficacy and safety of HBOT for PSD. Pooled results indicated that compared with control group, HBOT group was associated with a higher response rate. HBOT showed beneficial effect on depression severity, neurological deficit, physical disability. Besides, HBOT were associated with less AEs. The most frequent AEs for HBOT is ear pain due to barotrauma.

HAMD is the most commonly used scale to assess severity of depression [46]. There are three HAMD versions, 17-item, 21-item and 24-item version. In this study, severity of depression was quantified by HAMD 17-item version (in 21 studies) and HAMD 24-item version (in 4 studies). The pooled results suggested that HBOT was associated with more reduced HAMD scores, both in 17-item and 24-item versions, which implied HBOT could effectively alleviate depression symptoms. The mechanisms of HBOT for depression were not fully illuminated. Lim et al. inferred that HBOT affected depression-like behavior by attenuating neuroinflammation and inhibiting action on serotonin uptake [14]. A study by Sumen-Secgin et al. revealed that HBOT reduced the immobility time of rats and displayed an antidepressant-like activity [47]. Consistently, this meta-analysis provided evidence that HBOT could effectively attenuate depression.

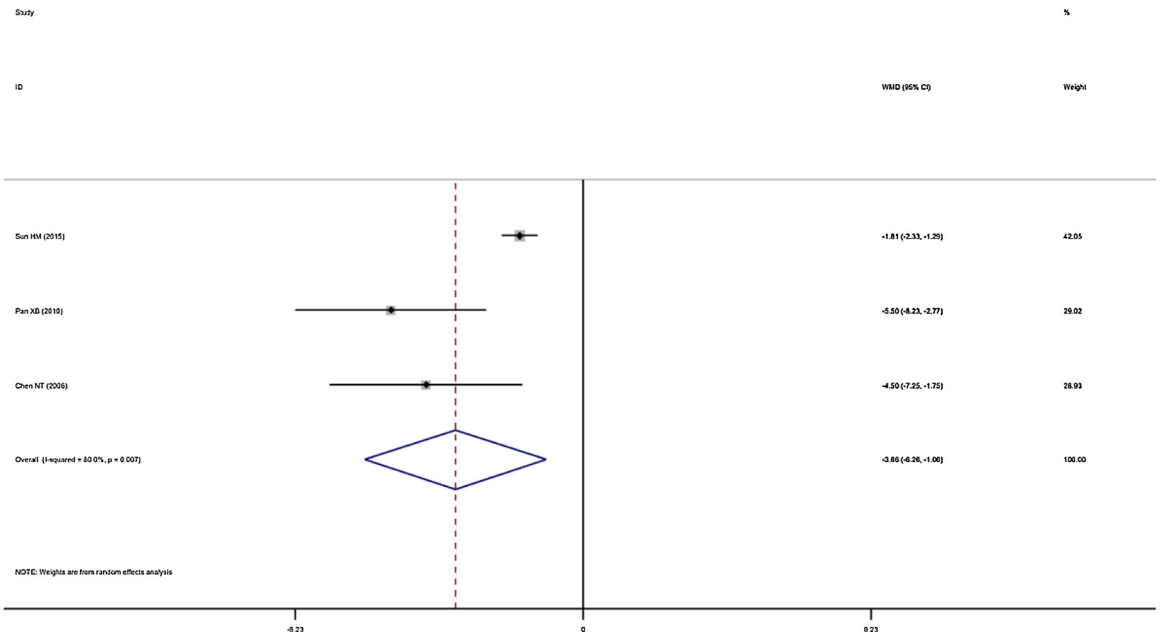

Fig. 8. Forest plot of MESSS score.

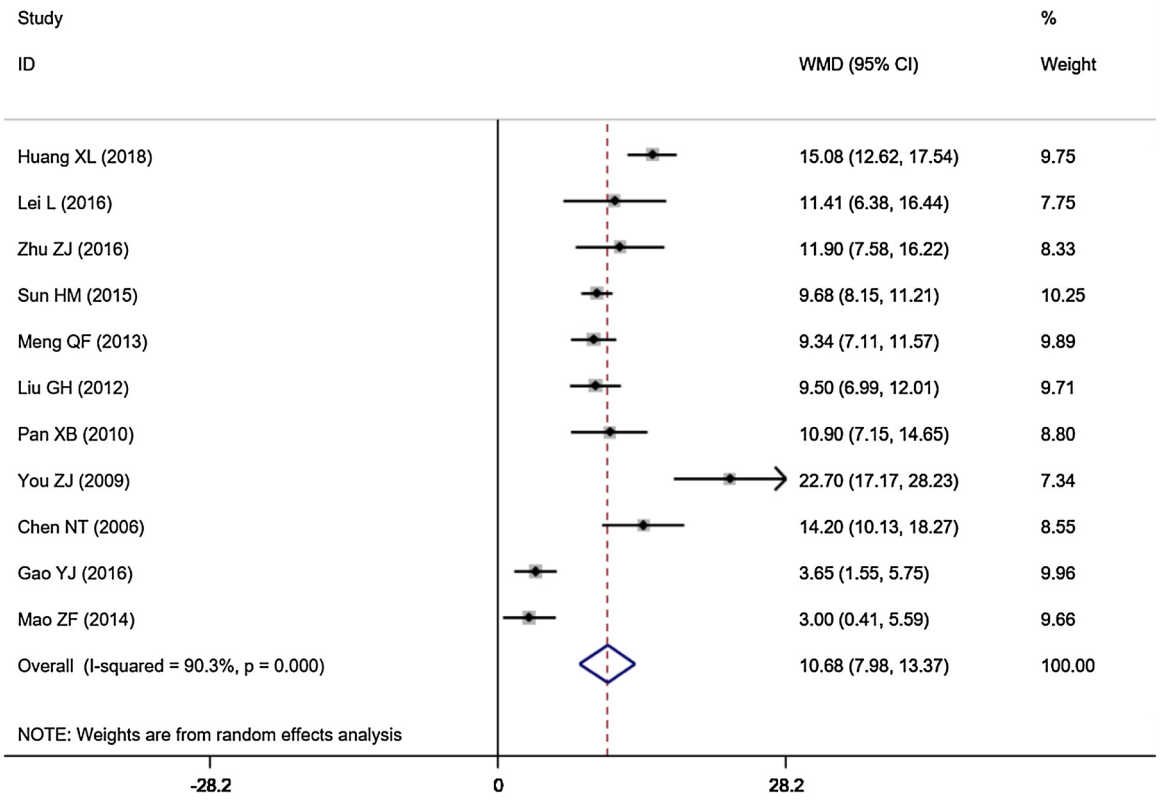

Fig. 9. Forest plot of BI.

Table 2
Effect of stroke type on HBOT outcomes.

Stroke type	Coef.	t-value	P-value
Response rate	0.14	3.96	0.011
HAMD-17 score	−4.54	−5.15	< 0.01
NIHSS score	−1.99	−0.20	0.848
BI score	3.33	10.25	< 0.01

Table 3
Effect of number of HBOT treatment.

Number of HBOT	Coef.	t-value	P-value
Response rate	0.27	0.03	0.979
HAMD-17 score	−4.25	−0.56	0.584
NIHSS score	−3.09	−0.29	0.779
BI score	10.79	1.10	0.297

Table 4
Effect of duration time of HBOT treatment.

Duration of HBOT	Coef.	t-value	P-value
Response rate	0.28	0.73	0.486
HAMD-17 score	−4.50	−14.25	< 0.01
NIHSS score	−3.34	−6.47	< 0.01
BI score	10.90	6.72	< 0.01

Table 5
Gender effect on HBOT outcome.

Gender effect	Coef.	t-value	P-value
Response rate	0.22	0.01	0.989
HAMD-17 score	−4.32	−0.33	0.748
NIHSS score	−3.22	−0.18	0.866
BI score	11.00	0.68	0.515

Our meta-analysis also suggested that HBOT patients were associated with a more reduced neurological deficit. In this study, the level of neurological deficit was quantified by three scales, NIHSS, CSS and MESSS. Most of neurologists worldwide use NIHSS scale to assess stroke severity. For PSD patients, a recent study revealed that NIHSS score was an independent risk factor of PSD patients both in acute and chronic stage of stroke [48]. Chinese Stroke Scale, also called CSS, was also an effective method to predict stroke severity of Chinese stroke survivors [49]. Modified Scandinavian stroke scale, also called MESSS, owns its advantages of simplification and less inter-rater variability, which was also widely used in neurological assessment. Consistently, our results indicated that HBOT were associated with a significantly more reduction in either NIHSS score, CSS score and MESSS score, which implied that HBOT could significantly attenuate neurological deficit. Several studies indicated that the level of neurological deficit was closely correlated with PSD development [50,51]. Particularly, stroke itself posed the risk of depression. Thus, HBOT maybe effective to treat PSD via healing neurological disability.

In addition, depression cause a worsen functional outcome and quality of life of stroke patients. Herein, we assessed patients' physical disability by using BI score. The pooled analysis demonstrated that HBOT significantly improved BI scores compared with control group, which implied that HBOT could benefit patients' physical function. Brown et al. suggested that BI measuring functional independence was consistently associated with PSD. Brown C highlighted the importance of helping PSD patients recover as much functional independence as possible in order to improve their life quality. In our analysis, HBOT significantly improve patients' BI scores, thus has a beneficial effect on patients' physical recovery.

This systematic review also assessed the safety of HBOT. The results

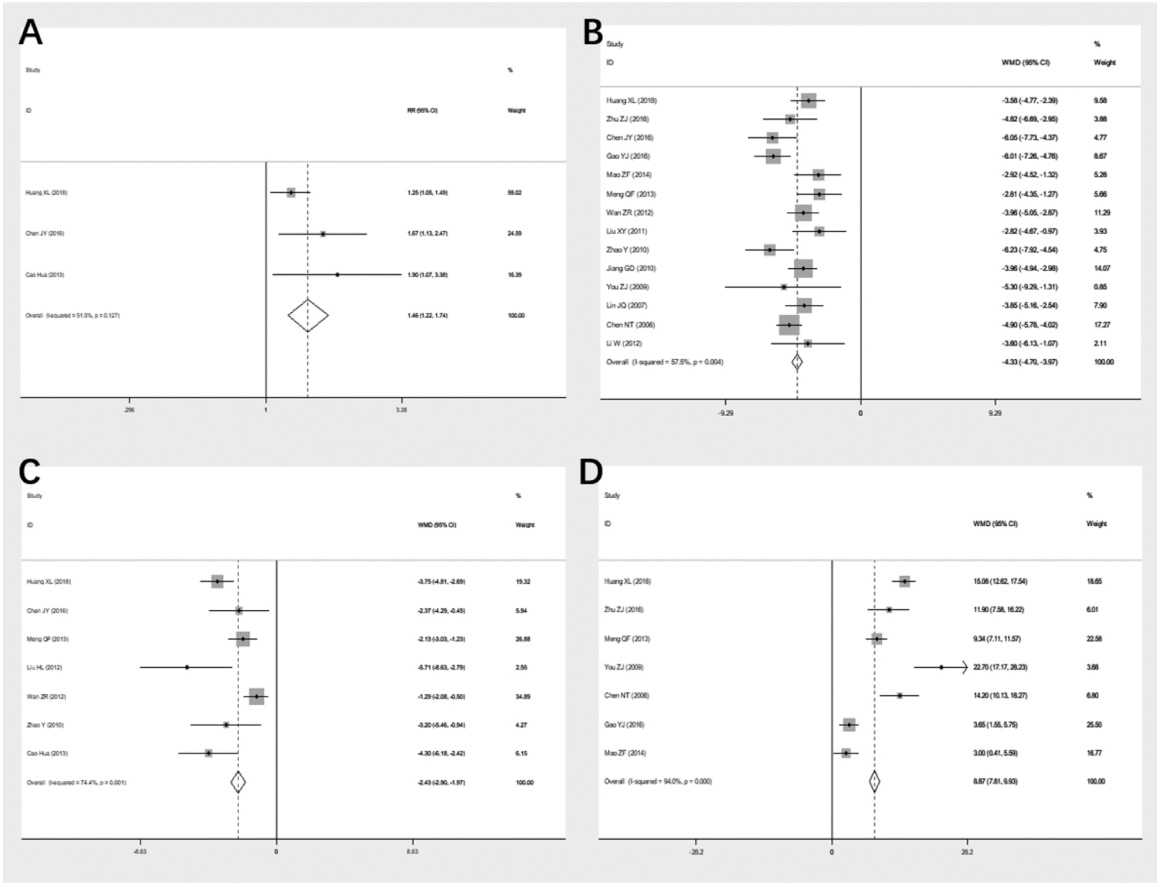

Fig. 10. Forest plot of (A) response rate; (B) HAMD 17-item score; (C) NIHSS score; (D) BI score with comparison between patients receiving HBOT plus antidepressants and patients receiving antidepressants alone.

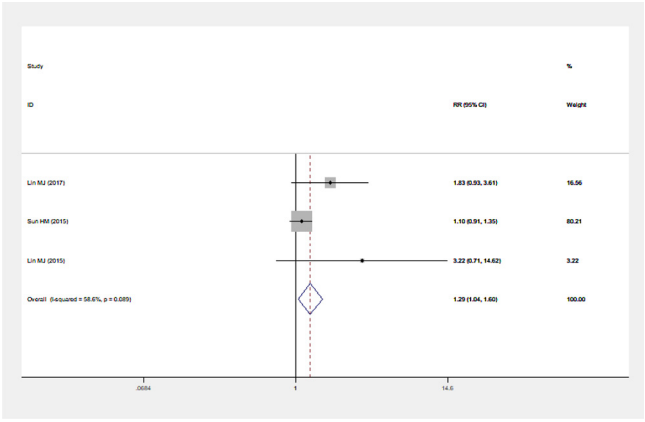

Fig. 11. Forest plot of response rate with comparison between patients receiving HBOT alone and patients receiving antidepressants alone.

showed that HBOT was associated with less AEs. As we know, a conundrum of AD therapy is its obvious side-effects. Besides, other complementary treatment, including psychotherapy and acupuncture, are largely influenced by a therapist's experiences, which lead to an uncertain efficacy. This study suggested that HBOT might be a more suitable therapeutic approach for PSD, with advantages of a superior effectiveness and safety.

In this meta-analysis, all included studies reports detailed patient selection by CT/MRI evaluation. Among these, sixteen studies reported stroke type of participants but only 2 studies reported location or side of lesions. By meta-regression analysis, our results revealed that participants with different stroke type achieved different response rate, HAMD-17 score and BI score after HBOT treatment. Subsequently we divided all included studies into two subgroups, Group A: studies with hemorrhage patients accounting for less than 20% and Group B: studies with hemorrhage patients accounting for no less than 20%. Subgroup analysis showed that the effect size was significantly different in two subgroups. Therefore, we speculate that patients with ischemic stroke may benefit more from HBOT treatment at least in reducing depression symptoms, as subgroup with hemorrhage patients accounting for less than 20% showed a more pronounced effect size of HAMD-17 score reduction. In addition to stroke type, we suggested that CT/MRI evaluation along with baseline HAMD, NIHSS, CSS and BI score altogether used to help patient selection. A study by Hadannyet al. revealed that HBOT induces significant improvements in all cognitive domains. They suggested that the selection of stroke patients for HBOT treatment should be based on functional imaging and baseline cognitive scores, rather than stroke type, location or side of lesion [52,53]. It is a limitation of our study that no functional analysis was described in all included studies. However, according to our meta-analysis, stroke type may be another consideration, which was inconsistent with results by Amir Hadanny et al. Further prospective study should be conducted to explore the effect of stroke type on HBOT outcomes.

The study has several other limitations. First, the methodological quality of included trials was relatively low. Second, most of included studies were with relatively small sample size. Third, we did not assess several laboratory parameters such as serum 5-hydroxytryptamine (5-HT) and norepinephrine (NE), which proven to have closely associations with depression. Forth, the results were largely affected by the subjectivity of outcome assessors in each study, as most outcome measures were based on "scale".

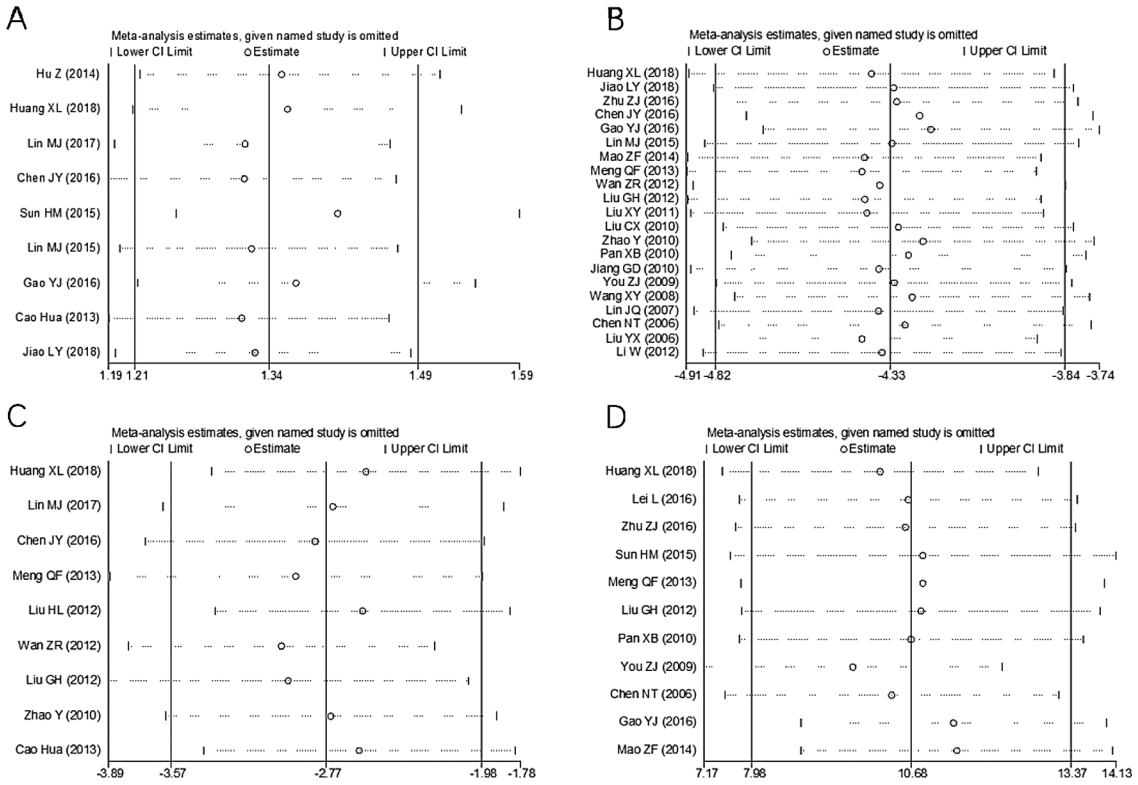

Fig. 12. Sensitivity analysis of (A) response rate; (B) HAMD 17-item score; (C) NIHSS score; (D) BI score.

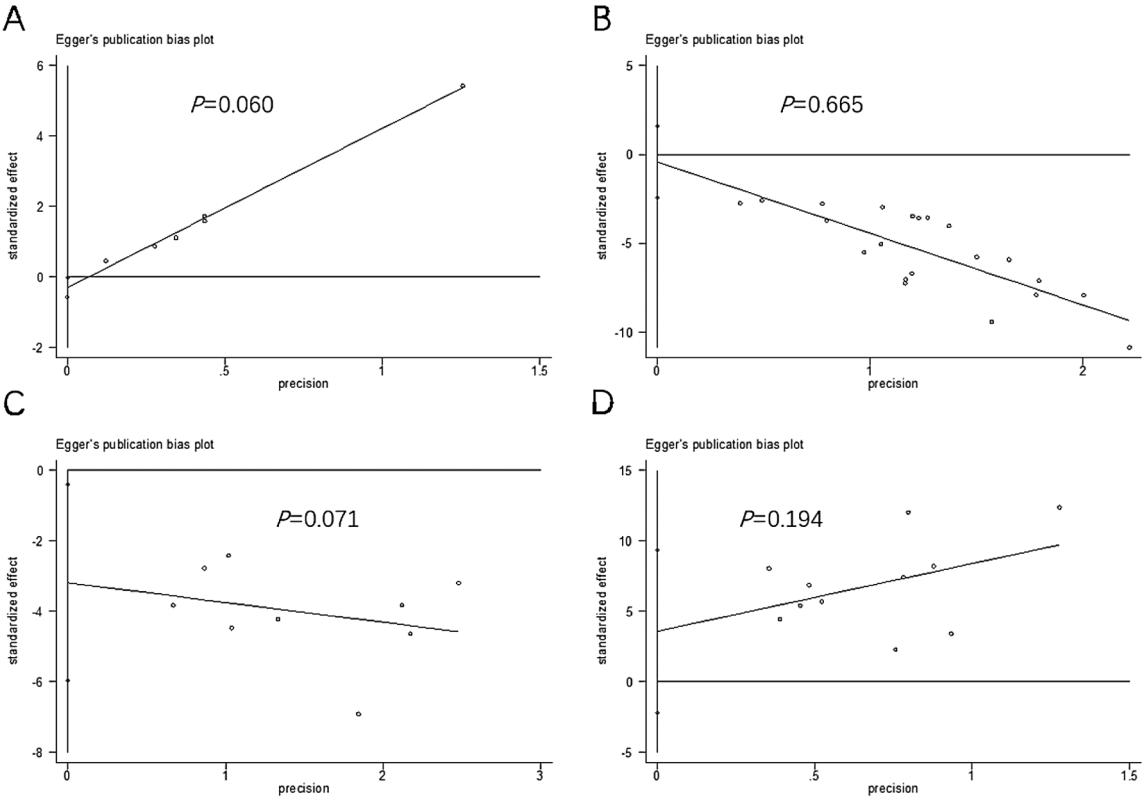

Fig. 13. Egger's test of (A) response rate; (B) HAMD 17-item score; (C) NIHSS score; (D) BI score.

5. Conclusions

In summary, this meta-analysis indicated that HBOT was associated with a higher response rate, reduced depression severity, attenuated neurological deficit, improved physical function and less adverse events for PSD patients. HBOT might be an efficacious therapeutic approach for PSD. However, the results should be cautiously interpreted due to relatively poor methodological quality of included studies.

Research involving human participants and/or animals

Not applicable.

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No.

Compliance with ethical standards

Disclosure of potential.

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CRediT authorship contribution statement

Xin-Xin Liang: Data curation, Writing - original draft. **You-guo Hao:** Visualization, Investigation. **Xue-ming Duan:** Supervision, Validation. **Xiu-lan Han:** Methodology, Software, Writing - review & editing. **Xiu-xia Cai:** Conceptualization, Methodology, Software.

Declaration of Competing Interest

The authors declare of none of conflict of interest.

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None.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.clineuro.2020.105910.

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